Improved Survival in Liver Transplant Patients Receiving Prolonged-Release Tacrolimus-Based Immunosuppression in the European Liver Transplant Registry (ELTR): An Extension Study

Adam, René ; Karam, Vincent ; Cailliez, Valérie ; et al ; Clavien, Pierre-Alain

Abstract: BACKGROUND We compared, through the European Liver Transplant Registry, long-term liver transplantation outcomes with prolonged-release tacrolimus (PR-T) versus immediate-release tacrolimus (IR-T)-based immunosuppression. This retrospective analysis comprises up to 8-year data collected between 2008 and 2016, in an extension of our previously published study. METHODS Patients with <1 month follow-up were excluded; patients were propensity score matched for baseline characteristics. Efficacy measures included: univariate/multivariate analyses of risk factors influencing graft/patient survival up to 8 years posttransplantation, and graft/patient survival up to 4 years with PR-T versus IR-T. Overall, 13 088 patients were included from 44 European centers; propensity score-matched analyses comprised 3006 patients (PR-T: n = 1002; IR-T: n = 2004). RESULTS In multivariate analyses, IR-T-based immunosuppression was associated with reduced graft survival (risk ratio, 1.49; P = 0.0038) and patient survival (risk ratio, 1.40; P = 0.0215). There was improvement with PR-T versus IR-T in graft survival (83% versus 77% at 4 y, respectively; P = 0.005) and patient survival (85% versus 80%; P = 0.017). Patients converted from IR-T to PR-T after 1 month had a higher graft survival rate than patients receiving IR-T at last follow-up (P < 0.001), or started and maintained on PR-T (P = 0.019). One graft loss in 4 years was avoided for every 14.3 patients treated with PR-T versus IR-T. CONCLUSIONS PR-T-based immunosuppression might improve long-term outcomes in liver transplant recipients than IR-T-based immunosuppression.

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Improved Survival in Liver Transplant Patients Receiving Prolonged-release Tacrolimus-based Immunosuppression in the European Liver Transplant Registry (ELTR): An Extension Study

René Adam, MD, PhD,[1] Vincent Karam, PhD,[1] Valérie Cailliez,[1] Pavel Trunečka, MD, PhD,[2] Didier Samuel, MD, PhD,[1] Giuseppe Tisone, MD, PhD,[3] Petr Němec, MD, PhD,[4] Olivier Soubrane, MD, PhD,[5] Stefan Schneeberger, MD, PhD,[6] Bruno Gridelli, MD, PhD,[7] Wolf O. Bechstein, MD, PhD,[8] Andrea Risaliti, MD, PhD,[9] Pal-Dag Line, MD, PhD,[10] Marco Vivarelli, MD, PhD,[11] Massimo Rossi, MD, PhD,[12] Jacques Pirenne, MD, PhD,[13] Jurgen L. Klempnauer, MD, PhD,[14] Aleh Rummo, MD, PhD,[15] Fabrizio Di Benedetto, MD, PhD,[16] Krzysztof Zieniewicz, MD, PhD,[17] Roberto Troisi, MD, PhD,[18] Andreas Paul, MD, PhD,[19] Toomas Vali, MD, PhD,[20] Otto Kollmar, MD, PhD,[21] Karim Boudjema, MD, PhD,[22] Emir Hoti, MD, PhD,[23] Michele Colledan, MD, PhD,[24] Johan Pratschke, MD, PhD,[25] Hauke Lang, MD, PhD,[26] Irinel Popescu, MD, PhD,[27] Bo-Goran Ericzon, MD, PhD,[28] Kestutis Strupas, MD, PhD,[29] Paolo De Simone, MD, PhD,[30] Eberhard Kochs, MD, PhD,[31] Bruno Heyd, MD, PhD,[32] Jean Gugenheim, MD, PhD,[33] Antonio D. Pinna, MD, PhD,[34] William Bennet, MD, PhD,[35] Mirjalal Kazimi, MD, PhD,[36] Philippe Bachellier, MD, PhD,[37] Stephen J. Wigmore, MD, PhD,[38] Allan Rasmussen, MD, PhD,[39] Pierre-Alain Clavien, MD, PhD,[40] Ernest Hidalgo, MD, PhD,[41] John G. O'Grady, MD, PhD,[42] Frausto Zamboni, MD, PhD,[43] Murat Kilic, MD, PhD,[44] and Christophe Duvoux, MD, PhD[45]; all contributing centers (www.eltr.org) and the European Liver and Intestine Transplant Association (ELITA)

Background. We compared, through the European Liver Transplant Registry, long-term liver transplantation outcomes with prolonged-release tacrolimus (PR-T) versus immediate-release tacrolimus (IR-T)–based immunosuppression. This retrospective analysis comprises up to 8-year data collected between 2008 and 2016, in an extension of our previously published study. **Methods.** Patients with <1 month follow-up were excluded; patients were propensity score matched for baseline characteristics. Efficacy measures included: univariate/multivariate analyses of risk factors influencing graft/patient survival up to 8 years posttransplantation, and graft/patient survival up to 4 years with PR-T versus IR-T. Overall, 13 088 patients were included from 44 European centers; propensity score–matched analyses comprised 3006 patients (PR-T: n = 1002; IR-T: n = 2004). **Results.** In multivariate analyses, IR-T-based immunosuppression was associated with reduced graft survival (risk ratio, 1.49; $P = 0.0038$) and patient survival (risk ratio, 1.40; $P = 0.0215$). There was improvement with PR-T versus IR-T in graft survival (83% versus 77% at 4 y, respectively; $P = 0.005$) and patient survival (85% versus 80%; $P = 0.017$). Patients converted from IR-T to PR-T after 1 month had a higher graft survival rate than patients receiving IR-T at last follow-up ($P < 0.001$), or started and maintained on PR-T ($P = 0.019$). One graft loss in 4 years was avoided for every 14.3 patients treated with PR-T versus IR-T. **Conclusions.** PR-T-based immunosuppression might improve long-term outcomes in liver transplant recipients than IR-T-based immunosuppression.

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[1] *Hepato-Biliary Center, AP-HP Paul Brousse Hospital, University of Paris-Sud, INSERM U935, Villejuif, France.*

[2] *Transplant Center, Institute for Clinical and Experimental Medicine (IKEM), Prague, Czech Republic.*

[3] *Liver Transplant Unit, Tor Vergata Polyclinic, University of Rome Tor Vergata, Rome, Italy.*

[4] *Center of Cardiovascular Surgery and Transplantation, Brno, Czech Republic.*

[5] *Department of Digestive Surgery, AP-HP Beaujon Hospital, Clichy, France.*

[6] *Department of Visceral, Transplant and Thoracic Surgery, Innsbruck Medical University, Innsbruck, Austria.*

[7] *Mediterranean Institute for Transplantation and Advanced Specialized Therapies, Palermo, Sicily, Italy.*

[8] *Department of General and Visceral Surgery, Goethe University Hospital and Clinics, Frankfurt, Germany.*

[9] *Department of Surgery, Liver Transplant Unit, University Hospital Udine, Udine, Italy.*

[10] *Department of Transplantation Medicine, Oslo University Hospital, Oslo, Norway.*

[11] *Hepatobiliary and Abdominal Transplantation Surgery, Department of Experimental and Clinical Medicine, Polytechnic University of Marche, Ancona, Italy.*

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Significant advances in the success of liver transplantation have been made over the past 2 decades, despite the increasing use of extended criteria donors.[1] However, although 1-year graft and patient survival rates in Europe are 77% and 83%, respectively, after a first liver transplantation, 10-year graft and patient survival rates remain lower at 54% and 61%, respectively.[2] Improving long-term liver transplant outcomes has, therefore, become a primary focus of the transplant community. Many factors can negatively influence outcomes in liver transplantation, including high Model for End-stage Liver Disease (MELD) scores and the viral status of the recipient (eg, hepatitis C virus [HCV] infection).[3,4] Nonadherence to immunosuppressive therapy and high intrapatient variability of drug exposure could also potentially reduce long-term transplant outcomes.[5-10]

Tacrolimus is now the cornerstone of immunosuppression after liver transplantation.[11] A once-daily, prolonged-release (PR) formulation of tacrolimus was licensed in Europe in 2007, for use in adult kidney or liver transplant recipients.[12] PR tacrolimus has demonstrated comparable efficacy to immediate-release (IR) tacrolimus in clinical studies with de novo liver transplant recipients and is efficacious following conversion of stable liver transplant recipients from IR to PR tacrolimus.[13-16] However, it is thought that the PR formulation may offer advantages over twice daily, IR tacrolimus, by reducing nonadherence to immunosuppressant medication and by decreasing intrapatient variability in tacrolimus exposure.[17-19] As both of these parameters have been associated with poor liver transplant outcomes,[8,20] treatment with PR tacrolimus has the potential to improve long-term outcomes for liver recipients, compared with the IR formulation. However, as clinical trials are of relatively short duration, there is a need for data to assess the effect of PR tacrolimus on long-term outcomes in liver transplantation. In this regard, registry studies can provide prospective and retrospective long-term data.

[12] Department of General Surgery, Organ Transplant Unit "Paride Stefanini", Umberto 1 Policlinico of Rome, Rome, Italy.

[13] Abdominal Transplant Surgery, University Hospital Leuven, Leuven, Belgium.

[14] Department of General, Visceral and Transplantation Surgery, Hannover Medical School, Hannover, Germany.

[15] Republican Scientific and Practical Center (RSPC) for Organ and Tissue Transplantation, Minsk, Belarus.

[16] Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit, University of Modena and Reggio Emilia, Modena, Italy.

[17] Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Warsaw, Poland.

[18] Department of General Hepato-Biliary and Liver Transplantation Surgery, Ghent University Hospital Medical School, Belgium.

[19] Department of General and Transplant Surgery, University Hospital Essen, Essen, Germany.

[20] Surgery Clinic, Tartu University Hospital, Tartu, Estonia.

[21] Department of General, Visceral and Pediatric Surgery, University Medical Center Göttingen, Göttingen, Germany.

[22] Department of Visceral Surgery, University Hospital Rennes, Pontchaillou Hospital, Rennes, France.

[23] Liver Unit, St. Vincent's Hospital, Dublin, Ireland.

[24] Department of Surgery, Pope John XXIII Hospital, Bergamo, Italy.

[25] Department of General, Visceral and Transplantation Surgery, Charité Campus Virchow-Klinikum (CVK), Berlin, Germany.

[26] General, Visceral and Transplantation Surgery Clinic, Johannes Gutenberg University Mainz, Mainz, Germany.

[27] Department of Surgery and Liver Transplantation, Fundeni Clinical Institute, University of Medicine "Carol Davila", Bucharest, Romania.

[28] Department of Transplantation Surgery, Karolinska University Hospital, Huddinge, Sweden.

[29] Department for Gastroentrology, Nephrology and Surgery, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania.

[30] Hepatobiliary Surgery and Liver Transplantation Unit, University of Pisa Medical School Hospital, Pisa, Italy.

[31] Surgical Clinic and Polyclinic, University Hospital Klinikum rechts der Isar Munich, Munich, Germany.

[32] Department of Visceral Surgery, University Hospital Besançon, University of Franche-Comté, Besançon, France.

[33] Department of Digestive Surgery, Archet 2 Hospital, Nice, France.

[34] University of Bologna, Transplant and HPB Institute, Bologna, Italy.

[35] Surgery Department, Transplantation and Liver Surgery Unit, Sahlgrenska University Hospital, Gothenburg, Sweden.

[36] Surgery and Organ Transplantation Center, Central Hospital of Oil Workers, Baku, Azerbaijan.

[37] Department of Surgery, Hospital Hautepierre, University Hospitals of Strasbourg, Strasbourg, France.

[38] Liver Transplantation Unit, University of Edinburgh Royal Infirmary, Edinburgh, United Kingdom.

[39] Department for Surgery and Transplantation, University Hospital Copenhagen, Copenhagen, Denmark.

[40] Department of Visceral and Transplant Surgery, University Hospital Zurich, Zurich, Switzerland.

[41] St James and Seacroft University Hospital, Leeds, United Kingdom.

[42] Liver Unit, King's College Hospital, London, United Kingdom.

[43] Department of General Surgery and Transplantation, Hospital G. Brotzu, Cagliari, Italy.

[44] Kent Hospital, Izmir, Turkey.

[45] Department of Hepatology and Gastroenterology, University Hospital of Henri-Mondor, Creteil, France.

P.T. has received speaker honorarium from Pfizer and has been involved in advisory boards and received consultancy agreements from Astellas. D.S. has received consultant fees from Astellas, Novartis, and Roche. P.N. has received speaker honoraria from Astellas and Novartis. W.O.B. has received honoraria and served on advisory boards for Astellas. M.V. and M.C. have received honorarium for an advisory board for Novartis. J.L.K. has received support from Astellas, Novartis, Roche, BMS, and Genzyme. B.G.E. has received speaker honorarium from Pfizer, Astellas, and Novartis. P.D.S. has received speaker fees and served as an advisory board member for Astellas. C.D. has received grants from Astellas, grants from Novartis, grants and other from Chiesi, personal fees from Sandoz, and nonfinancial support from Biotest. The other authors declare no conflict of interests.

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Correspondence: René Adam, MD, PhD, Centre Hépatobiliaire, Hôpital Paul Brousse, Avenue Paul Vaillant Couturier, 94804 Villejuif, France. (rene.adam@aphp.fr).

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The impact of PR versus IR tacrolimus on long-term graft and patient survival was recently assessed using data from the European Liver Transplant Registry (ELTR) in 528 and 3839 patients receiving PR or IR tacrolimus, respectively.[21] The study was conducted at 21 European centers between 2008 and 2012.[21] Multivariable analyses showed that the use of IR tacrolimus was associated with a higher risk of graft loss (risk ratio, 1.81; $P = 0.001$) and patient death (risk ratio, 1.72; $P = 0.004$) compared with PR tacrolimus.[21] We report here an analysis of up to 8-year data, collected between 2008 and 2016, in an extension of the previously published study, with the aim of comparing long-term liver transplant outcomes with PR versus IR tacrolimus–based immunosuppression. We also studied the outcome of converting patients from one formulation of the drug to the other, during the posttransplantation follow-up period.

MATERIALS AND METHODS

This was a retrospective analysis of primary liver transplant patients receiving PR tacrolimus (Advagraf; Astellas Pharma Europe BV, The Netherlands) and IR tacrolimus in the ELTR database, as previously described.[21] The ELTR currently represents liver transplant data from 174 transplant centers across Europe. Data from participating centers are collected on a voluntary basis at regular intervals using a 2-part, standardized questionnaire designed by the ELTR Coordinating Committee to capture information on donors and recipients, as described previously.[21] The methods used to populate the registry and obtain the data have been described elsewhere.[22-24] To prevent center bias, only the 44 centers who used both PR and IR tacrolimus at the time of the study were eligible for inclusion in this analysis.

Inclusion Criteria

Data were collected prospectively from patients (aged ≥18 y) who underwent their first liver transplant between January 2008 and June 2016 from contributing centers across Europe. All patients included in this study received PR or IR tacrolimus, with or without concomitant immunosuppressants (including induction agents) within the first month after liver transplantation.

Clinical Efficacy Measures

Efficacy measures were analyzed using the modified intent-to-treat population, which excluded all patients who had <1 month of follow-up after transplantation. This strategy aimed to avoid the potential impact of early postoperative complications not associated with the immunosuppressive regimen. The clinical efficacy measures included univariate and multivariate analyses of the risk factors influencing graft and patient survival; Kaplan-Meier estimates of the incidence of graft and patient survival stratified by PR and IR tacrolimus–based immunosuppression, and causes of graft loss and mortality. Treatment groups were stratified by PR or IR tacrolimus treatment during the first month after transplantation, and patients remained in these allocated groups, regardless of any changes in immunosuppression during follow-up. However, crossover changes from IR to PR and vice versa after 1 month of therapy, regardless of the date of change(s), were considered to measure their impact on graft and patient outcomes. The maintenance immunosuppression data considered in this study were those collected at the last patient follow-up. The number of patients needed to treat with PR versus IR tacrolimus to avoid 1 graft loss in 4 years was calculated. To adjust for the number of patients at risk over the enrollment time between 2008 and 2016 (fewer patients at risk in the PR than IR tacrolimus group at 4 y owing to the gradual increase in the use of PR tacrolimus), the era of transplantation was added to the univariate and multivariate analyses.

Propensity Score Matching

To account for differences in donor and recipient baseline characteristics between groups when estimating the effect of treatment on outcomes, the clinical efficacy measures were repeated on a propensity score–matched population. PR and IR tacrolimus groups were paired on a 1:2 ratio according to 18 items with similar values. The propensity score was based on recipient age (≥60 versus <60 y), donor age (≥60 versus <60 y), full-size organ from a donor after brain death versus all other alternative grafts (living donor, domino, donation after circulatory death, or split grafts from a donor after brain death), MELD score (>24 versus ≤24), recipient hepatitis B virus (HBV) surface antigen, hepatocellular carcinoma (HCC), presence of severe ascites before liver transplantation, United Network for Organ Sharing (UNOS) status (3–4 versus 1–2), total ischemia time (≥6 versus <6 h), graft preservation solution histidine-tryptophan-ketoglutarate versus all other solutions (University Wisconsin, Celsior, IGL-1, Marshall, Ringer, Solution de conservation des Organes et des Tissus [SCOT], or other), and administration of other immunosuppressive medications early posttransplantation (corticosteroids, mycophenolate mofetil, ciclosporin, basiliximab, daclizumab, sirolimus, everolimus, azathioprine). For continuous variables that were converted to discontinuous variables in the model (eg, donor age, recipient age, MELD score), the values that were the most discriminant between PR and IR tacrolimus were selected as cutoffs, based on the calculation of chi-square value and odds ratios (data not shown). All unmatched units in the PR and IR tacrolimus groups were excluded from the propensity score–matched population.

Statistical Analyses

Statistical analyses were conducted as previously described.[21] A univariate Cox regression analysis was performed to evaluate the risk factors influencing graft and patient survival after liver transplantation. Data from the univariate analyses were reported using log-rank P values, with $P < 0.05$ considered to be statistically significant. A Cox proportional hazards regression evaluation ($P < 0.15$) was used in a multivariate model to assess the impact of donor and recipient variables on graft and patient survival. Patients with missing data on the ELTR questionnaire were excluded from the multivariate analyses. Kaplan-Meier analyses were used to estimate graft and patient survival stratified by treatment group; statistical analyses were performed using the log-rank test ($P < 0.05$). Analyses were performed using SAS Enterprise Guide version 5.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Donor and Recipient Characteristics and Demographics

Patient Population

In the initial ELTR study, 4367 primary liver transplant recipients (PR tacrolimus: n = 528; IR tacrolimus: n = 3839) were included in the analysis, between 2008 and 2012.[21] In this extension analysis, 13 088 primary liver transplant recipients were included (Figure 1). All patients received either PR tacrolimus (n = 1762) or IR tacrolimus (n = 11 326). Since PR tacrolimus was licensed for use in 2007,[12] the proportion of patients who received PR tacrolimus during month 1 gradually increased over enrollment (between 2008 and 2016).

Baseline Characteristics

Baseline characteristics of donors and recipients are presented in Table 1. Mean recipient age was greater in the PR versus IR tacrolimus group (52.1 ± 18.7 versus 51.8 ± 18.1 y, respectively; $P < 0.001$). The other main characteristics and their differences between groups are shown in Table 1.

Concomitant Medications

Baseline tacrolimus-associated induction immunosuppressive medications were different in the 2 groups: corticosteroids (69.2% versus 61.4%; $P < 0.001$), everolimus (7.5% versus 2.5%; $P < 0.001$), mycophenolate mofetil (75.1% versus 55.8%; $P < 0.001$), and daclizumab (1.8% versus 0.8%; $P < 0.001$) were more frequently combined with PR tacrolimus. Azathioprine (3.2% versus 0.5%; $P < 0.001$), ciclosporin (1.6% versus 0.2%; $P < 0.001$), basiliximab 25.4% versus 22.0%; $P = 0.002$), and sirolimus (0.6% versus 0.2%; $P = 0.026$) were more frequently combined with IR tacrolimus. However, propensity score matching has been used to account for these baseline differences in our study.

Analyses of Patients With ≥1 Month of Follow-up

Univariate Analyses

In the univariate analysis, IR tacrolimus during the first month posttransplantation was identified as a significant risk factor for inferior graft survival ($P < 0.001$) and patient survival ($P = 0.003$) over 8 years. Other factors that significantly contributed to reduced long-term graft and patient survival are listed in Table 2.

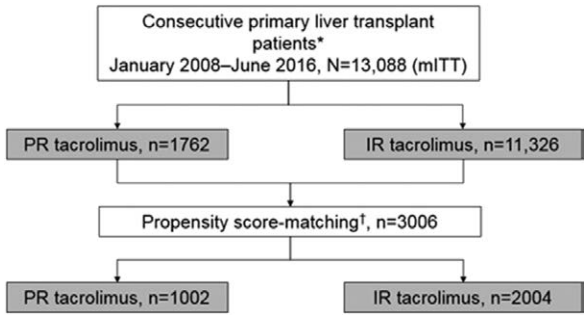

FIGURE 1. Patient populations. *Analysis only in centers using prolonged-release (PR) tacrolimus and immediate-release (IR) tacrolimus. †Propensity score matching ratio 1:2, PR tacrolimus/IR tacrolimus. mITT, modified intent to treat.

Kaplan-Meier Analyses

Kaplan-Meier analysis demonstrated significantly improved graft and patient survival over 4 years with PR versus IR tacrolimus (84% versus 79%; $P < 0.001$ and 85% versus 81%; $P = 0.003$, respectively) (Figure 2). At year 4, a 5% and 4% improvement in graft and patient survival, respectively, was observed in the PR versus IR tacrolimus group.

Propensity Score–matched Analyses

The propensity score–matched analysis was performed on 3006 patients (PR tacrolimus: n = 1002; IR tacrolimus: n = 2004). Donor and recipient baseline characteristics were generally comparable between the 2 treatment groups for the propensity score–matched patients, especially for the concomitant immunosuppressive drugs combined with tacrolimus (Table 1).

Univariate and Multivariate Analyses

In the univariate analysis, the use of IR tacrolimus was a significant risk factor for reduced graft and patient survival ($P = 0.005$ and $P = 0.017$, respectively) in addition to other factors listed in Table 3. Long-term graft survival was significantly impacted by 13 additional factors: donor age ≥50 years ($P < 0.001$), recipient age ≥50 years ($P = 0.006$), recipient dialysis twice in week before transplantation ($P = 0.016$), negative HBV delta ($P = 0.017$), positive anti-HCV serology ($P < 0.001$), positive human immunodeficiency virus serology ($P = 0.028$), positive HCV RNA ($P < 0.001$), urgent liver transplant ($P = 0.038$), UNOS status 1 or 2 ($P < 0.001$), serum creatinine concentration ≥2 mg/dL ($P = 0.01$), Milan criteria-out in patients with HCC ($P < 0.001$), HCC with tumor size >50 mm ($P < 0.001$), and heterotopic liver transplant ($P = 0.003$).

Long-term patient survival was significantly impacted by 15 other factors: donor age ≥50 years ($P < 0.001$), presence of macro/microvesicular graft steatosis ($P = 0.039$), male recipient ($P = 0.021$), recipient age ≥50 years ($P = 0.001$), recipient dialysis twice in week before transplantation ($P = 0.006$), negative HBV delta ($P = 0.025$), positive anti-HCV serology ($P < 0.001$), positive human immunodeficiency virus serology ($P = 0.045$), positive HCV RNA ($P < 0.001$), UNOS status 1 or 2 ($P < 0.001$), serum creatinine concentration ≥2 mg/dL ($P = 0.001$), cancer as main indication ($P = 0.032$), Milan criteria-out in patients with HCC ($P < 0.001$), HCC with tumor size >50 mm ($P < 0.001$), and heterotopic liver transplant ($P = 0.001$).

In the multivariate analysis (Table 4), the use of IR tacrolimus was a significant independent risk factor for reduced graft survival (risk ratio: 1.49; 95% confidence interval [CI]: 1.14-1.96; $P = 0.0038$) associated with 5 other factors: recipient positive anti-HCV serology (risk ratio: 2.05; 95% CI: 1.66-2.54; $P < 0.001$), recipient age ≥50 years (risk ratio: 1.74; 95% CI: 1.43-2.11; $P < 0.001$), UNOS status 1 or 2 (risk ratio: 1.69; 95% CI: 1.35-2.11; $P < 0.001$), serum creatinine concentration ≥2 mg/dL (risk ratio: 1.66; 95% CI: 1.18-2.35; $P = 0.004$), and donor age ≥50 years (risk ratio: 1.35; 95% CI: 1.09-1.66; $P = 0.005$).

The use of IR tacrolimus was also a significant independent risk factor for reduced patient survival (risk ratio, 1.40; 95% CI, 1.05-1.86; $P = 0.0215$) associated with 6 other factors: recipient positive anti-HCV serology (risk ratio,

TABLE 1.

Baseline characteristics of donors and liver transplant recipients

		mITT population			Propensity score–matched patients[a]		
Parameter	**Category**	**PR tacrolimus (n = 1762)[b]**	**IR tacrolimus (n = 11 326)[b]**	***P*[c]**	**PR tacrolimus (n = 1002)[b]**	**IR tacrolimus (n = 2004)[b]**	***P*[c]**
Donor characteristics							
Mean (SD) age, y		52.1 (18.7) (n = 1743)	51.8 (18.1) (n = 11 018)	0.49	53.0 (18.7)	53.5 (18.7)	0.56
	≥60, n (%)	666 (38.2)	3923 (35.6)	0.035	401 (40.0)	806 (40.2)	0.92
	≥65, n (%)	486 (27.9)	2933 (26.6)	0.27	294 (29.3)	631 (31.5)	0.23
	≥75, n (%)	198 (11.4)	1188 (10.8)	0.47	135 (13.5)	284 (14.2)	0.60
Sex, n (%)							
	Female	754 (43.3)	4874 (44.5)	0.34	449 (45.0)	876 (44.0)	0.57
	Male	987 (56.7)	6072 (55.5)		548 (55.0)	1117 (56.0)	
Recipient characteristics							
Age at first transplant (y)	Mean (SD)	53.7 (11.2)	52.3 (11.6)	<0.001	53.1 (11.4)	53.3 (10.8)	0.68
	≥60, n (%)	584 (33.1)	3176 (28)	<0.001	308 (30.7)	603 (30.1)	0.72
	≥65, n (%)	242 (13.7)	1169 (10.3)	<0.001	115 (11.5)	223 (11.1)	0.78
	≥70, n (%)	31 (1.8)	135 (1.2)	0.048	22 (2.2)	22 (1.1)	0.018
Sex, n (%)	Female	571 (32.4)	3783 (33.4)	0.41	328 (32.7)	623 (31.1)	0.36
	Male	1191 (67.6)	7542 (66.6)		674 (67.3)	1381 (68.9)	
Mean (SD) BMI, kg/m^2		25.9 (4.7) (n = 1660)	25.9 (4.8) (n = 10 714)	0.97	25.8 (4.8) (n = 970)	25.6 (4.5) (n = 1934)	0.20
Recipient health status and indication for transplant							
HBsAg, n (%)	Negative	1486 (91.1)	9130 (87.9)	<0.001	908 (90.6)	1810 (90.3)	0.79
	Positive	146 (8.9)	1261 (12.1)		94 (9.4)	194 (9.7)	
HBV DNA, n (%)	Negative	422 (92.3)	3613 (89.7)	0.079	316 (92.7)	605 (92.2)	0.80
	Positive	35 (7.7)	413 (10.3)		25 (7.3)	51 (7.8)	
Coexisting HBV and delta virus, n (%)	Negative	316 (91.9)	1956 (87.3)	0.016	202 (92.7)	373 (86.9)	0.029
	Positive	28 (8.1)	284 (12.7)		16 (7.3)	56 (13.1)	
Anti-HCV serology, n (%)	Negative	1230 (76.1)	7798 (75.3)	0.48	762 (77.4)	1431 (72.9)	0.008
	Positive	387 (23.9)	2564 (24.7)		222 (22.6)	532 (27.1)	
HCV RNA, n (%)	Negative	292 (61.9)	2699 (66.8)	0.03	217 (63.8)	466 (63.2)	0.85
	Positive	180 (38.1)	1339 (33.2)		123 (36.2)	271 (36.8)	
HIV serology, n (%)	Negative	1179 (98.1)	9821 (98.5)	0.24	825 (97.7)	1805 (98.6)	0.12
	Positive	23 (1.9)	147 (1.5)		19 (2.3)	26 (1.4)	
Main indication for transplant, n (%)	Acute liver disease	111 (6.4)	631 (5.8)	<0.001	62 (6.3)	80 (4.1)	0.046
	Malignant tumors	501 (28.8)	2637 (24.0)		246 (24.9)	511 (25.9)	
	Chronic liver disease	1004 (57.7)	6694 (61.0)		600 (60.7)	1224 (62.1)	
	Benign tumors	45 (2.6)	244 (2.2)		27 (2.7)	36 (1.8)	
	Metabolic diseases	64 (3.7)	583 (5.3)		46 (4.7)	95 (4.8)	
	Other	16 (0.9)	178 (1.6)		8 (0.8)	26 (1.3)	
HCC (primary or secondary disease), n (%)	No	1210 (69.1)	8163 (72.5)	0.003	715 (71.4)	1397 (69.7)	0.35
	Yes	542 (30.9)	3092 (27.5)		287 (28.6)	607 (30.3)	

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TABLE 1. (Continued)

Parameter	Category	mITT population			Propensity score–matched patients[a]		
		PR tacrolimus (n = 1762)[b]	IR tacrolimus (n = 11 326)[b]	P[c]	PR tacrolimus (n = 1002)[b]	IR tacrolimus (n = 2004)[b]	P[c]
Liver transplant urgency[d], n (%)	Yes	99 (7.0)	701 (7.7)	0.35	65 (9.1)	99 (7.0)	0.093
	No	1309 (93.0)	8346 (92.3)		651 (90.9)	1311 (93.0)	
UNOS status[e], n (%)	1	110 (6.7)	1026 (9.7)	<0.001	77 (7.7)	170 (8.5)	0.76
	2	176 (10.7)	1505 (14.2)		141 (14.1)	272 (13.6)	
	3	765 (46.4)	5848 (55.0)		594 (59.3)	1162 (58.0)	
	4	596 (36.2)	2245 (21.1)		190 (19.0)	400 (20.0)	
Mean (SD) MELD score		17.1 (8.5) (n = 1725)	17.9 (9.0) (n = 11 040)	<0.001	17.6 (8.9)	17.6 (8.8)	0.97
Liver function and baseline laboratory values							
Child-Pugh class, n (%)	A	100 (16.2)	899 (14.1)	0.085	73 (16.6)	165 (16.1)	0.82
	B	279 (45.1)	3166 (49.6)		203 (46.2)	492 (48.0)	
	C	240 (38.8)	2322 (36.4)		163 (37.1)	367 (35.8)	
Mean (SD) serum creatinine concentration, mg/dL		1.1 (1.5) (n = 1742)	1.2 (3.8) (n = 11 078)	0.23	1.1 (1.8) (n = 999)	1.1 (0.9) (n = 1993)	0.97
Mean (SD) total bilirubin, mg/dL		5.7 (8.2) (n = 1718)	6.2 (9.0) (n = 11 038)	0.032	6.1 (8.6) (n = 999)	5.9 (8.7) (n = 1999)	0.44
Preservation solution, n (%)	HTK	816 (47.1)	3059 (28.0)	<0.001	380 (37.9)	691 (34.5)	0.063
	Other	915 (52.9)	7863 (72.0)		622 (62.1)	1313 (65.5)	
Induction immunosuppressive regimen							
Corticosteroids, n (%)	Yes	1219 (69.2)	6959 (61.4)	<0.001	777 (77.5)	1579 (78.8)	0.43
	No	543 (30.8)	4367 (38.6)		225 (22.5)	425 (21.2)	
Azathioprine, n (%)	Yes	9 (0.5)	358 (3.2)	<0.001	7 (0.7)	7 (0.3)	0.18
	No	1753 (99.5)	10 968 (96.8)		995 (99.3)	1997 (99.7)	
Ciclosporin, n (%)	Yes	4 (0.2)	180 (1.6)	<0.001	4 (0.4)	10 (0.5)	0.70
	No	1758 (99.8)	11 146 (98.4)		998 (99.6)	1994 (99.5)	
Everolimus, n (%)	Yes	133 (7.5)	280 (2.5)	<0.001	49 (4.9)	128 (6.4)	0.10
	No	1629 (92.5)	11 046 (97.5)		953 (95.1)	1876 (93.6)	
Basiliximab, n (%)	Yes	387 (22.0)	2875 (25.4)	0.002	274 (27.3)	518 (25.8)	0.38
	No	1375 (78.0)	8451 (74.6)		728 (72.7)	1486 (74.2)	
Sirolimus, n (%)	Yes	3 (0.2)	66 (0.6)	0.026	1 (0.1)	1 (0.0)	0.62
	No	1759 (99.8)	11 260 (99.4)		1001 (99.9)	2003 (100.0)	
MMF, n (%)	Yes	1323 (75.1)	6316 (55.8)	<0.001	762 (76.0)	1504 (75.0)	0.55
	No	439 (24.9)	5010 (44.2)		240 (24.0)	500 (25.0)	
Daclizumab, n (%)	Yes	31 (1.8)	87 (0.8)	<0.001	23 (2.3)	47 (2.3)	0.93
	No	1731 (98.2)	11 239 (99.2)		979 (97.7)	1957 (97.7)	
Mean (SD) length of follow-up, mo		25.6 (21.1)	31.5 (26.0)	<0.001	24.4 (19.9)	33.7 (25.4)	<0.001

[a]Propensity score matching was based on recipient age (≥60 vs <60 y), donor age (≥60 vs <60 y), full-size organ from a donor after brain death vs all other alternative grafts (living donor, domino, donation after circulatory death, or split grafts from a donor after brain death), MELD score (>24 vs ≤24), recipient hepatitis B virus surface antigen, HCC, presence of severe ascites before liver transplantation, UNOS status (3–4 vs 1–2), total ischemia time (≥6 vs <6 h), graft preservation solution HTK versus all other solutions (University Wisconsin, Belzer, Celsior, IGL-1, Marshall, Ringer, Solution de conservation des Organes et des Tissus [SCOT], or other), and administration of other immunosuppressive medications early posttransplantation (corticosteroids, MMF, ciclosporin, basiliximab, daclizumab, sirolimus, everolimus, azathioprine).
[b]Data were not available for all patients; therefore, percentages are calculated based on available data.
[c]*P* value between treatment cohort comparisons.
[d]Liver transplant urgency was determined by the treating physician and indicated on the questionnaire by "yes" or "no" tick box.
[e]UNOS status: 1. Hospitalized in the intensive care unit, 2. Continuous hospitalization, 3. Continuous medical care, 4. At home with normal function.
BMI, body mass index; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTK, histidine–tryptophan-ketoglutarate; IR, immediate release; MELD, Model for End-stage Liver Disease; mITT, modified intent to treat; MMF, mycophenolate mofetil; PR, prolonged release; UNOS, United Network for Organ Sharing.

TABLE 2.

Univariate analyses of risk factors for reduced graft and patient survival 1, 2, and 4 y posttransplantation, after exclusion of patients with <1 mo of follow-up (mITT population)

Parameters at first transplantation	Category	n	Survival, %			P[a]
			1 y	2 y	4 y	
Graft survival						
Immunotherapy during mo 1	PR tacrolimus	1762	93	89	84	<0.001
	IR tacrolimus	11 326	91	86	79	
Donor characteristics						
Donor sex	Female	5628	91	86	79	0.51
	Male	7059	91	87	79	
Donor age ≥50 y	Yes	7272	90	85	77	<0.001
	No	5488	93	89	83	
Donor age ≥60 y	Yes	4589	90	84	76	<0.001
	No	8171	92	88	81	
Macro/microvesicular graft steatosis	No	3286	93	89	82	0.11
	Yes	2947	91	88	80	
Blood group compatibility	Compatible	794	88	83	77	<0.001
	Isogroup	11 983	91	87	80	
	Noncompatible	113	77	72	59	
Recipient characteristics						
Recipient sex	Female	4354	92	88	81	<0.001
	Male	8733	91	86	78	
Recipient age ≥50 y	Yes	8693	90	86	78	<0.001
	No	4395	92	89	82	
Recipient age ≥60 y	Yes	3760	89	85	77	<0.001
	No	9328	92	88	81	
Recipient dialysis (twice in week prior)	Yes	442	81	78	71	<0.001
	No	11 177	92	87	80	
Recipient viral status						
HBsAg	Negative	10 616	91	87	79	0.008
	Positive	1407	94	88	83	
Coexisting HBV and delta virus	Negative	2272	90	85	79	0.001
	Positive	312	96	93	91	
Anti-HCV serology	Negative	9028	92	89	82	<0.001
	Positive	2951	88	82	72	
HIV serology	Negative	11 000	91	87	80	<0.001
	Positive	170	82	71	61	
HCV RNA	Negative	2991	92	88	83	<0.001
	Positive	1519	88	83	71	
Criteria for liver transplant						
Liver transplant urgency[b]	Yes	800	89	86	81	0.74
	No	9655	91	87	80	
UNOS status[c]	1	1136	87	83	77	<0.001
	2	1681	88	84	78	
	3	6613	92	88	80	
	4	2841	93	88	80	
UNOS status[c] 1 or 2	Yes	2817	87	84	78	<0.001
	No	9454	92	88	80	
MELD score	≤14	5571	93	87	79	<0.001
	15–25	4938	92	88	82	
	>25	2256	87	83	76	
Liver function and laboratory values						
Recipient Child-Pugh class	A	999	92	88	79	0.1
	B	3445	94	90	82	
	C	2562	91	88	80	
Serum creatinine concentration ≥2 mg/dL	Yes	906	83	79	73	<0.001
	No	11 914	92	88	80	

Continued next page

TABLE 2. (Continued)

Parameters at first transplantation	Category	n	Survival, %			P[a]
			1 y	2 y	4 y	
Indication						
Main indication for transplant	Acute liver failure	742	90	86	81	<0.001
	Chronic liver disease	7698	91	87	80	
	Metabolic disease	647	90	87	80	
	Tumor (benign)	289	94	92	88	
	Tumor (malignant)	3138	92	85	76	
	Other	194	87	83	79	
Acute liver failure as main disease	Yes	725	90	86	81	0.2
	No	12 282	91	87	79	
Cirrhosis as main disease	Yes	6935	91	87	80	0.9
	No	6072	91	86	79	
Cancer as main disease	Yes	3133	92	85	76	<0.001
	No	9874	91	87	81	
Milan criteria (in patients with HCC)	Yes	1613	93	88	81	<0.001
	No	808	87	76	61	
HCC with tumor size >50 mm	Yes	214	82	65	48	<0.001
	No	2228	91	86	76	
Surgical procedure						
Total ischemia time, h	>15	103	90	88	83	0.25
	12–15	623	89	84	78	
	6–12	8325	91	87	79	
	0–6	2409	92	86	80	
Total ischemia time ≥12 h	Yes	726	89	85	78	0.53
	No	10 734	91	87	79	
Type of graft	Full size (donor brain death)	11 390	91	87	79	0.4
	Domino	89	91	84	70	
	Living	520	91	83	75	
	Reduced	36	88	88	88	
	Split	526	90	88	82	
	After circulatory death	486	93	87	80	
Liver transplant	Heterotopic	15	100	88	72	0.67
	Orthotopic	12 424	91	87	80	
Patient survival						
Immunotherapy during mo 1	PR tacrolimus	1762	94	90	85	0.003
	IR tacrolimus	11 319	92	88	81	
Donor characteristics						
Donor sex	Female	5623	92	88	81	0.48
	Male	7057	92	88	82	
Donor age ≥50 y	Yes	7268	91	87	79	<0.001
	No	5485	94	90	85	
Donor age ≥60 y	Yes	4587	91	86	78	<0.001
	No	8166	93	89	84	
Macro/microvesicular graft steatosis	No	3284	94	91	85	0.01
	Yes	2943	92	89	82	
Blood group compatibility	Compatible	793	89	84	78	<0.001
	Isogroup	11 977	92	89	82	
	Noncompatible	113	80	77	63	
Recipient characteristics						
Recipient sex	Female	4353	93	90	84	<0.001
	Male	8727	92	88	81	
Recipient age ≥50 y	Yes	8689	91	87	80	<0.001
	No	4392	94	91	85	
Recipient age ≥60 y	Yes	3758	90	86	78	<0.001
	No	9323	93	89	83	

Continued next page

TABLE 2. (Continued)

Parameters at first transplantation	Category	n	Survival, %			P[a]
			1 y	2 y	4 y	
Recipient dialysis (twice in week prior)	Yes	442	82	79	74	<0.001
	No	11 170	93	89	83	
Recipient viral status						
HBsAg	Negative	10 612	92	88	82	0.007
	Positive	1406	95	90	85	
Coexisting HBV and delta virus	Negative	2272	91	86	80	<0.001
	Positive	312	96	94	92	
Anti-HCV serology	Negative	9023	93	90	84	<0.001
	Positive	2949	89	84	75	
HIV serology	Negative	10 995	93	89	82	<0.001
	Positive	169	82	74	64	
HCV RNA	Negative	2991	93	90	85	<0.001
	Positive	1518	90	84	74	
Criteria for liver transplant						
Liver transplant urgency[b]	Yes	800	90	88	86	0.43
	No	9648	93	89	82	
UNOS status[c]	1	1135	88	85	81	<0.001
	2	1680	89	85	80	
	3	6612	94	90	82	
	4	2837	94	90	83	
UNOS status[c] 1 or 2	Yes	2815	88	85	80	<0.001
	No	9449	94	90	83	
MELD score	≤14	5569	94	89	81	<0.001
	15–25	4934	93	90	84	
	>25	2255	88	85	79	
Liver function and laboratory values						
Recipient Child-Pugh class	A	999	95	90	82	0.05
	B	3442	95	91	85	
	C	2560	92	89	84	
Serum creatinine concentration ≥2 mg/dL	Yes	905	84	80	75	<0.001
	No	11 908	93	89	82	
Indication						
Main indication for transplant	Acute liver failure	742	90	87	85	<0.001
	Chronic liver disease	7694	92	89	82	
	Metabolic disease	647	91	88	82	
	Tumor (benign)	289	95	94	91	
	Tumor (malignant)	3138	93	86	77	
	Other	194	89	86	80	
Acute liver failure as main disease	Yes	725	90	87	85	0.16
	No	12 275	92	88	81	
Cirrhosis as main disease	Yes	6931	92	89	82	0.63
	No	6069	93	88	81	
Cancer as main disease	Yes	3133	93	86	77	<0.001
	No	9867	92	89	83	
Milan criteria (in patients with HCC)	Yes	1613	94	89	83	<0.001
	No	808	88	77	62	
HCC with tumor size >50 mm	Yes	214	82	66	50	<0.001
	No	2228	93	87	78	
Total ischemia time, h	>15	103	90	88	85	0.59
	12–15	622	91	87	81	
	6–12	8319	92	89	82	
	0–6	2409	93	88	82	
Total ischemia time ≥12 h	Yes	725	91	87	81	0.94
	No	10 728	92	88	82	

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TABLE 2. (Continued)

Parameters at first transplantation	Category	n	Survival, %			P[a]
			1 y	2 y	4 y	
Type of graft	Full size (donor brain death)	11 387	92	88	81	0.005
	Domino	89	91	87	73	
	Living	520	92	84	78	
	Reduced	36	100	96	96	
	Split	526	93	90	86	
	After circulatory death	482	96	91	85	
Liver transplant	Heterotopic	15	100	88	72	0.5
	Orthotopic	12 417	92	89	82	

[a]Log-rank *P* value for effect over 8 y.
[b]Liver transplant urgency was determined by the treating physician and indicated on the questionnaire by "yes" or "no" tick box.
[c]UNOS status: 1. Hospitalized in the intensive care unit, 2. Continuous hospitalization, 3. Continuous medical care, 4. At home with normal function.
HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTK, histidine–tryptophan-ketoglutarate; IR, immediate release; MELD, Model for End-stage Liver Disease; mITT, modified intent to treat; MMF, mycophenolate mofetil; PR, prolonged release; UNOS, United Network for Organ Sharing.

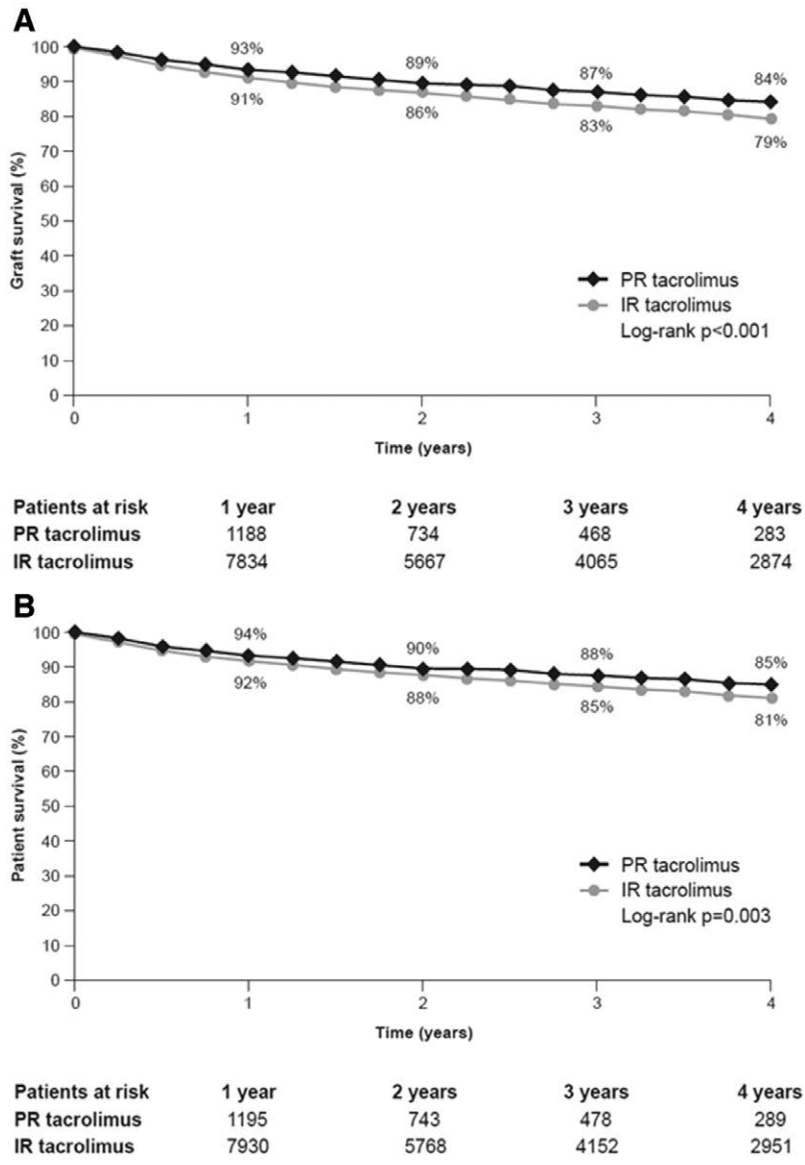

FIGURE 2. Kaplan-Meier analyses of (A) graft and (B) patient survival over 4 y of treatment with prolonged-release (PR) tacrolimus compared with immediate-release (IR) tacrolimus, after exclusion of patients with <1 mo of follow-up (modified intent-to-treat population).

TABLE 3.

Univariate analyses of risk factors for reduced graft and patient survival for propensity score–matched patients

Parameters at first transplant	Category	n	Survival, %			P[a]
			1 y	2 y	4 y	
Graft survival						
Immunotherapy during mo 1	PR tacrolimus	1002	93	89	83	0.005
	IR tacrolimus	2004	90	86	77	
Donor characteristics						
Donor sex	Female	1325	92	87	79	0.55
	Male	1665	91	88	80	
Donor age ≥50 y	Yes	1776	90	85	76	<0.001
	No	1230	93	90	84	
Donor age ≥60 y	Yes	1207	90	84	75	<0.001
	No	1799	92	89	82	
Macro/microvesicular graft steatosis	No	597	93	90	81	0.069
	Yes	604	90	86	77	
Blood group compatibility	Compatible	182	85	81	74	0.19
	Isogroup	2799	92	88	79	
	Noncompatible	23	85	77	77	
Recipient characteristics						
Recipient sex	Female	951	92	88	80	0.064
	Male	2055	91	87	78	
Recipient age ≥50 y	Yes	2065	91	86	77	0.006
	No	941	93	89	83	
Recipient age ≥60 y	Yes	911	90	85	76	0.016
	No	2095	92	88	80	
Recipient dialysis twice in week before transplantation	Yes	124	83	77	73	0.016
	No	2685	92	88	79	
Recipient viral status						
HBsAg	Negative	2718	91	87	79	0.37
	Positive	288	93	88	83	
Coexisting HBV and delta virus	Negative	575	89	84	73	0.017
	Positive	72	98	95	95	
Anti-HCV serology	Negative	2193	92	89	83	<0.001
	Positive	754	88	82	67	
HIV serology	Negative	2630	91	87	79	0.028
	Positive	45	91	76	66	
HCV RNA	Negative	683	91	87	84	<0.001
	Positive	394	88	80	63	
Criteria for liver transplant						
Liver transplant urgency[b]	Yes	164	84	81	79	0.038
	No	1962	92	88	80	
UNOS status[c]	1	247	88	83	80	<0.001
	2	413	84	79	73	
	3	1756	93	89	81	
	4	590	93	89	77	
UNOS status[c] 1 or 2	Yes	660	86	81	75	<0.001
	No	2346	93	89	80	
MELD score	≤14	1326	93	88	77	0.47
	15–25	1159	91	87	81	
	>25	521	89	85	79	
Liver function and laboratory values						
Recipient Child-Pugh class	A	238	94	90	82	0.37
	B	695	93	90	81	
	C	530	90	86	79	
Serum creatinine concentration ≥2 mg/dL	Yes	185	87	80	74	0.01
	No	2807	92	88	80	

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TABLE 3. (Continued)

Parameters at first transplant	Category	n	Survival, %			P^a
			1 y	2 y	4 y	
Indication						
Main indication for transplant	Acute liver failure	142	89	85	85	0.45
	Chronic liver disease	1824	91	88	80	
	Metabolic disease	141	89	86	78	
	Tumor (benign)	63	95	88	84	
	Tumor (malignant)	757	93	86	75	
	Other	34	85	85	79	
Acute liver failure as main disease	Yes	140	89	85	85	0.33
	No	2866	92	87	79	
Cirrhosis as main disease	Yes	1648	91	88	79	0.86
	No	1358	92	87	79	
Cancer as main disease	Yes	756	93	86	75	0.1
	No	2250	91	88	80	
Milan criteria (in patients with HCC)	Yes	550	93	87	79	<0.001
	No	224	88	79	60	
HCC with tumor size >50 mm	Yes	63	83	65	46	<0.001
	No	715	92	86	76	
Surgical procedure						
Total ischemia time, h	>15	17	82	82	82	0.39
	12–15	128	84	79	78	
	6–12	2186	91	87	79	
	0–6	675	93	88	81	
Total ischemia time ≥12 h	Yes	145	84	80	78	0.47
	No	2861	92	88	79	
Type of graft	Full size (donor brain death)	2712	91	87	79	0.65
	Domino	28	93	85	65	
	Living	77	87	83	83	
	Reduced	13	92	92	92	
	Split	116	93	92	85	
	After circulatory death	60	94	87	87	
Liver transplant	Heterotopic	4	100	67		0.003
	Orthotopic	2857	92	87	79	
Patient survival						
Immunotherapy during mo 1	PR tacrolimus	1002	94	90	85	0.017
	IR tacrolimus	2004	92	88	80	
Donor characteristics						
Donor sex	Female	1325	92	87	80	0.18
	Male	1665	93	89	83	
Donor age ≥50 y	Yes	1776	91	86	78	<0.001
	No	1230	94	92	86	
Donor age ≥60 y	Yes	1207	92	86	77	<0.001
	No	1799	93	90	84	
Macro/microvesicular graft steatosis	No	597	93	91	85	0.039
	Yes	604	92	88	78	
Blood group compatibility	Compatible	182	85	81	75	0.11
	Isogroup	2799	93	89	82	
	Noncompatible	23	90	83	83	
Recipient characteristics						
Recipient sex	Female	951	93	90	83	0.021
	Male	2055	92	88	80	
Recipient age ≥50 y	Yes	2065	92	88	79	0.001
	No	941	93	90	86	
Recipient age ≥60 y	Yes	911	91	86	77	0.001
	No	2095	93	89	83	

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TABLE 3. (Continued)

Parameters at first transplant	Category	n	Survival, %			P[a]
			1 y	2 y	4 y	
Recipient dialysis (twice in week prior)	Yes	124	83	77	73	0.002
	No	2685	93	89	82	
Recipient viral status						
HBsAg	Negative	2718	92	88	81	0.3
	Positive	288	94	90	85	
Coexisting HBV and delta virus	Negative	575	90	85	76	0.025
	Positive	72	98	95	95	
Anti-HCV serology	Negative	2193	93	90	84	<0.001
	Positive	754	89	83	71	
HIV serology	Negative	2630	92	88	81	0.045
	Positive	45	91	80	70	
HCV RNA	Negative	683	92	89	85	<0.001
	Positive	394	88	81	67	
Criteria for liver transplant						
Liver transplant urgency[b]	Yes	164	84	84	81	0.099
	No	1962	93	89	82	
UNOS status[c]	1	247	89	85	82	<0.001
	2	413	85	81	74	
	3	1756	94	90	83	
	4	590	94	90	80	
UNOS status[c] 1 or 2	Yes	660	87	83	77	<0.001
	No	2346	94	90	82	
MELD score	≤14	1326	94	89	79	0.22
	15–25	1159	92	89	84	
	>25	521	90	86	80	
Liver function and laboratory values						
Recipient Child-Pugh class	A	238	96	91	84	0.27
	B	695	94	91	83	
	C	530	90	87	81	
Serum creatinine concentration ≥2 mg/dL	Yes	185	88	80	75	0.001
	No	2807	93	89	82	
Indication						
Main indication for transplant	Acute liver failure	142	90	87	87	0.24
	Chronic liver disease	1824	92	89	82	
	Metabolic disease	141	90	87	78	
	Tumor (benign)	63	95	92	89	
	Tumor (malignant)	757	93	87	77	
	Other	34	91	91	85	
Acute liver failure as main disease	Yes	140	90	87	87	0.34
	No	2866	92	88	81	
Cirrhosis as main disease	Yes	1648	92	89	82	0.61
	No	1358	93	88	81	
Cancer as main disease	Yes	756	93	87	77	0.032
	No	2250	92	89	83	
Milan criteria (in patients with HCC)	Yes	550	94	88	81	<0.001
	No	224	89	80	62	
HCC with tumor size >50 mm	Yes	63	83	66	48	<0.001
	No	715	93	87	78	
Total ischemia time, h	>15	17	82	82	82	0.31
	12–15	128	85	80	79	
	6–12	2186	92	89	81	
	0–6	675	94	90	83	
Total ischemia time ≥12 h	Yes	145	85	80	79	0.26
	No	2861	93	89	81	

Continued next page

TABLE 3. (Continued)

Parameters at first transplant	Category	n	Survival, % 1 y	2 y	4 y	P[a]
Type of graft	Full size (donor brain death)	2712	92	88	81	0.57
	Domino	28	93	89	69	
	Living	77	89	89	89	
	Reduced	13	100	100		
	Split	116	94	93	88	
	After circulatory death	60	98	91	86	
Liver transplant	Heterotopic	4	100	67		0.001
	Orthotopic	2857	92	89	81	

[a]Log-rank *P* value for effect over 8 y.
[b]Body mass index was defined as underweight: <18.5 kg/m^2, normal weight: 18.5–24.9 kg/m^2, overweight: 25.0–29.9 kg/m^2, and obesity: ≥30 kg/m^2.
[c]Liver transplant urgency was determined by the treating physician and indicated on the questionnaire by "yes" or "no" tick box.
[d]UNOS status: 1. Hospitalized in the intensive care unit, 2. Continuous hospitalization, 3. Continuous medical care, 4. At home with normal function.
HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IR, immediate release; MELD, Model for End-stage Liver Disease; PR, prolonged release; UNOS, United Network for Organ Sharing.

1.91; 95% CI, 1.52-2.40; $P < 0.001$), serum creatinine concentration ≥2 mg/dL (risk ratio, 1.90; 95% CI, 1.33-2.71; $P < 0.001$), UNOS status 1 or 2 (risk ratio, 1.89; 95% CI, 1.49-2.39; $P < 0.001$), recipient age ≥50 years (risk ratio, 1.74; 95% CI, 1.41-2.16; $P < 0.001$), HCC as primary or secondary disease (risk ratio, 1.35; 95% CI, 1.07-1.69; $P = 0.01$), and donor age ≥50 years (risk ratio, 1.33; 95% CI, 1.07-1.66; $P = 0.01$).

Kaplan-Meier Analyses and Number of Patients Needed to Treat to Avoid 1 Graft Loss

Kaplan-Meier analysis demonstrated significantly improved graft and patient survival over 4 years with PR versus IR tacrolimus (83% versus 77%; $P = 0.005$ and 85% versus 80%; $P = 0.017$, respectively) (Figure 3). At year 4, a 6% and 5% improvement in graft and patient survival, respectively, was observed in the PR versus IR tacrolimus group. The number of patients needed to treat with PR versus IR tacrolimus to avoid 1 graft loss in 4 years was 14.3 patients (95% CI, 9.7-27.3).

Analysis of Crossover Groups

In the nonconverted patients over the study period, graft and patient survival were significantly higher with (induction-last follow-up immunosuppressive regimen available) PR-PR than with IR-IR tacrolimus (88% versus 82% at 4 y; $P = 0.019$ and 89% versus 83% at 4 y; $P = 0.047$, respectively) (Figure 4). Patients converted from IR to PR tacrolimus after 1 month had a significantly higher graft and patient survival rate compared with patients who were started on and still receiving PR tacrolimus at the last follow-up (92% versus 88% at 4 y; $P = 0.019$ and 94% versus 89% at 4 y; $P = 0.004$, respectively) or started on and still receiving IR tacrolimus at the last follow-up ($P < 0.001$ for both).

Causes of Graft Loss and Mortality

The most common cause of graft loss was infection in both groups (Table 5). Over 8 years of treatment, the proportion of patients with bacterial infection that resulted in graft loss was higher with PR versus IR tacrolimus

TABLE 4.

Multivariate analyses of risk factors for reduced graft and patient survival for the propensity score–matched patients

Risk factors at first transplant	Risk ratio	95% Confidence interval	P
Graft survival			
Recipient anti-HCV serology positive	2.05	1.66-2.54	<0.001
Recipient age ≥55 y	1.74	1.43-2.11	<0.001
UNOS status[a] 1 or 2	1.69	1.35-2.11	<0.001
Serum creatinine concentration ≥2 mg/dL	1.66	1.18-2.35	0.004
IR tacrolimus immunotherapy	1.49	1.14-1.96	0.0038
Donor age ≥50 y	1.35	1.09-1.66	0.0052
Patient survival			
Recipient anti-HCV serology positive	1.91	1.52-2.40	<0.001
Serum creatinine concentration ≥2 mg/dL	1.90	1.33-2.71	<0.001
UNOS status[a] 1 or 2	1.89	1.49-2.39	<0.001
Recipient age ≥55 y	1.74	1.41-2.16	<0.001
IR tacrolimus immunotherapy	1.40	1.05-1.86	0.0215
HCC (primary or secondary disease)	1.35	1.07-1.69	0.0109
Donor age ≥50 y	1.33	1.07-1.66	0.0110

[a]UNOS status 1: Hospitalized in the intensive care unit; 2: Continuous hospitalization. N = 3883.
HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IR, immediate release; UNOS, United Network for Organ Sharing.

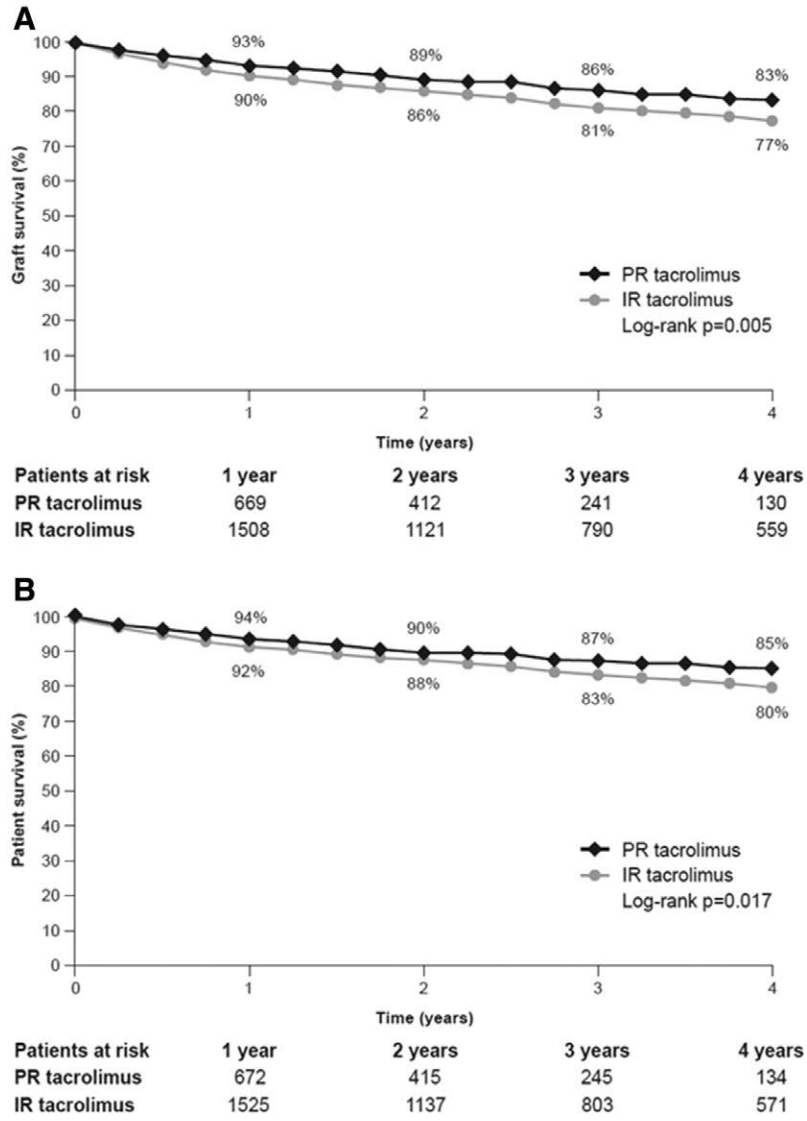


FIGURE 3. Kaplan-Meier analyses of (A) graft and (B) patient survival over 4 y of treatment with prolonged-release (PR) tacrolimus compared with immediate-release (IR) tacrolimus for the propensity score–matched patients.

(17.2% versus 9.2%, respectively; $P = 0.031$) (Table 5). Compared with patients receiving IR tacrolimus, "other" causes of graft loss were less frequent in patients receiving PR tacrolimus ($P = 0.01$). However, there were no significant differences between groups in the incidence of graft loss due to acute or chronic rejection, cardiovascular, or renal causes.

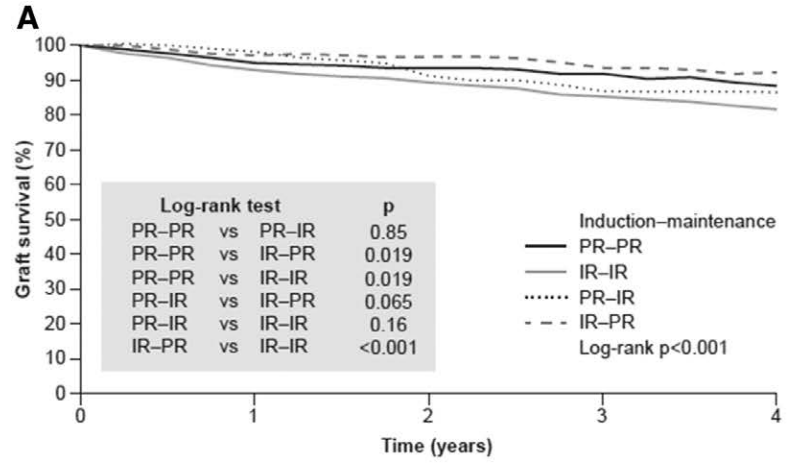
The most common cause of patient mortality was infection in both groups (Table 5). The proportion of patients with bacterial infection that resulted in patient death was similar with PR and IR tacrolimus (18.3% versus 10.4%, respectively; $P = 0.057$). "Other" causes of mortality were less frequent in patients receiving PR versus IR tacrolimus ($P = 0.005$). There were no significant differences between treatment groups in the proportion of patients with cardiovascular or renal causes of mortality.

DISCUSSION

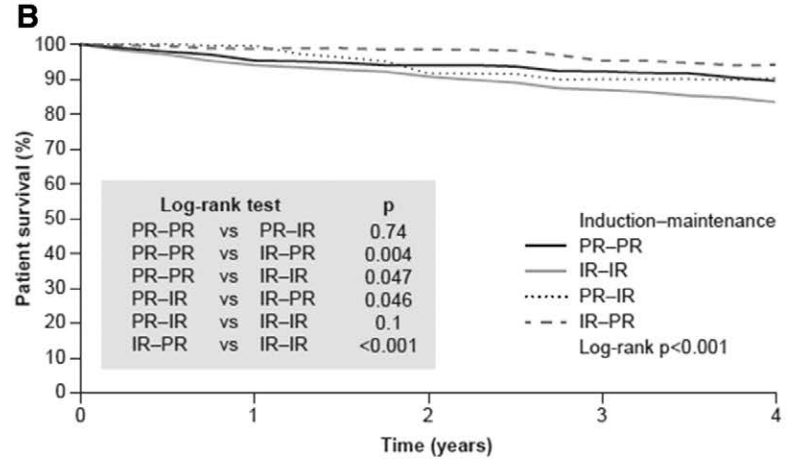
The initial ELTR study was the first large retrospective registry study in Europe, evaluating PR tacrolimus–based immunosuppression in primary liver transplantation.[21] The study showed that the use of IR tacrolimus was associated with a higher risk of graft loss and patient death, compared with PR tacrolimus. Additionally, PR tacrolimus significantly improved graft and patient survival over 3 years posttransplantation, compared with the IR formulation.[21] However, the cohort size was relatively limited, as was the length of follow-up.

This extension to the ELTR study, reporting up to 8-year data from adult primary liver transplant recipients, confirmed that PR tacrolimus was associated with improved graft and patient survival (over 4 y posttransplantation), compared with IR tacrolimus. Consistent with Adam et al,[21] IR tacrolimus was an independent risk factor for graft loss and mortality over 8 years of treatment. In addition to the longer time period assessed, the number of patients included in the current study exceeded 13 000, compared with the 4367 patients included in the initial ELTR study.[21] This provided enhanced statistical robustness, increasing the reliability of the results.

Univariate and multivariate analyses substantiated the independent prognostic value of typical risk factors,



Survival, %		1 year	2 years	3 years	4 years
PR–PR		95	93	92	88
PR–IR		98	91	87	87
IR–PR		97	97	93	92
IR–IR		93	89	86	82
Patients at risk	Total				
PR–PR	560	417	270	177	105
PR–IR	176	142	91	45	16
IR–PR	274	254	214	167	124
IR–IR	1074	879	668	486	348



Survival, %		1 year	2 years	3 years	4 years
PR–PR		95	94	92	89
PR–IR		99	91	90	90
IR–PR		99	98	95	94
IR–IR		94	91	87	83
Patients at risk	Total				
PR–PR	560	418	272	178	106
PR–IR	176	144	92	48	19
IR–PR	274	258	217	168	125
IR–IR	1074	888	679	495	355

FIGURE 4. Kaplan-Meier analyses of (A) graft and (B) patient survival over 4 y of treatment in crossover groups for the propensity score–matched patients. IR, immediate release; PR, prolonged release.

including donor age (≥50 y), recipient viral status (HCV positivity), and UNOS status 1 or 2 in impairing month 1 to year 8 graft and patient survival.[25,26] As reported by Adam et al,[21] IR tacrolimus was also identified in this study as a significant predictor of graft loss and patient death in univariate analyses. Furthermore, after accounting for differences in baseline characteristics between treatment groups, IR tacrolimus formulation remained a significant

TABLE 5.

Causes of graft loss and mortality over 8 years of treatment for the propensity score–matched patients

		Graft loss, n (%)				Mortality, n (%)			
Category	**Type**	**All (n = 3006)**	**PR tacrolimus (n = 1002)**	**IR tacrolimus (n = 2004)**	***P*[a]**	**All (n = 3006)**	**PR tacrolimus (n = 1002)**	**IR tacrolimus (n = 2004)**	***P*[a]**
Overall		408	93	315	–	351	82	269	–
Technical complications	All	44 (10.8)	12 (12.9)	32 (10.2)	0.45	19 (5.4)	6 (7.3)	13 (4.8)	0.38
	Biliary	21 (5.2)	6 (6.5)	15 (4.8)	0.39	12 (3.4)	4 (4.9)	8 (3.0)	0.41
	Vascular	24 (5.9)	6 (6.5)	18 (5.7)	0.79	8 (2.3)	2 (2.4)	6 (2.2)	1.00
Rejection	All	16 (3.9)	3 (3.2)	13 (4.1)	1.00	8 (2.3)	2 (2.4)	6 (2.2)	1.00
	Acute	5 (1.2)	1 (1.1)	4 (1.3)	1.00	3 (0.9)	1 (1.2)	2 (0.7)	0.55
	Chronic	11 (2.7)	2 (2.2)	9 (2.9)	1.00	5 (1.4)	1 (1.2)	4 (1.5)	1.00
Nontumoral recurrence		76 (18.6)	22 (23.7)	54 (17.1)	0.16	57 (16.2)	19 (23.2)	38 (14.1)	0.06
Other liver complications		13 (3.2)	3 (3.2)	10 (3.2)	1.00	12 (3.4)	3 (3.7)	9 (3.4)	1.00
Tumor	Tumor recurrence	49 (12.0)	13 (14.0)	36 (11.4)	0.51	48 (13.7)	13 (15.9)	35 (13.0)	0.51
	De novo tumor	50 (12.3)	10 (10.8)	40 (12.7)	0.62	50 (14.2)	10 (12.2)	40 (14.9)	0.54
	De novo tumor (lymph)	3 (0.7)	1 (1.1)	2 (0.6)	0.54	3 (0.9)	1 (1.2)	2 (0.7)	0.55
Infection	Overall	109 (26.7)	28 (30.1)	81 (25.7)	0.40	107 (30.5)	27 (32.9)	80 (29.7)	0.58
	Bacterial	45 (11.0)	16 (17.2)	29 (9.2)	0.031	43 (12.3)	15 (18.3)	28 (10.4)	0.057
	Viral	1 (0.2)	0	1 (0.3)	1.00	1 (0.3)	0	1 (0.4)	1.00
	Fungal	2 (0.5)	1 (1.1)	1 (0.3)	0.40	2 (0.6)	1 (1.2)	1 (0.4)	0.41
	Undefined	67 (16.4)	13 (14.0)	54 (17.1)	0.47	66 (18.8)	12 (14.6)	54 (20.1)	0.27
General	Gastrointestinal	13 (3.2)	3 (3.2)	10 (3.2)	1.00	13 (3.7)	3 (3.7)	10 (3.7)	1.00
	Cardiovascular	18 (4.4)	5 (5.4)	13 (4.1)	0.57	18 (5.1)	5 (6.1)	13 (4.8)	0.58
	Cerebrovascular	13 (3.2)	6 (6.5)	7 (2.2)	0.08	13 (3.7)	6 (7.3)	7 (2.6)	0.09
	Renal	15 (3.7)	3 (3.2)	12 (3.8)	1.00	15 (4.3)	3 (3.7)	12 (4.5)	1.00
	Pulmonary	31 (7.6)	7 (7.5)	24 (7.6)	0.98	31 (8.8)	7 (8.5)	24 (8.9)	0.91
Other		66 (16.2)	7 (7.5)	59 (18.7)	0.010	62 (17.7)	6 (7.3)	56 (20.8)	0.005
Social cause		3 (0.7)	1 (1.1)	2 (0.6)	0.54	3 (0.9)	1 (1.2)	2 (0.7)	0.55
Suicide		1 (0.2)	0	1 (0.3)	1.00	1 (0.3)	0	1 (0.4)	1.00

[a]*P* value for Mantel-Haenszel chi-square test between treatment cohort comparisons or Fisher exact test, as appropriate. Data are presented for up to 3 causes of graft loss or patient mortality for each patient.
IR, immediate release; PR, prolonged release.

predictor of graft and patient loss, in both univariate and multivariate analyses.

In the previous ELTR study, improvements in graft and patient survival with PR versus IR tacrolimus were observed as early as 3 months after transplantation and continued over 3 years.[21] Our current data demonstrate that the survival benefit associated with PR tacrolimus continues over 4 years of treatment. Furthermore, while improved 3-year patient survival with PR versus IR tacrolimus did not reach statistical significance for the unmatched patient cohort in the initial ELTR study,[21] the benefit was statistically significant by year 4 in our current study. Indeed, there was a 5% and 4% graft and patient survival advantage, respectively, by year 4 with the PR versus IR formulation. The difference between the PR and IR groups for graft and patient survival rates also seemed to increase with time.

Consistent with data reported in a 4-year follow-up of de novo liver transplant recipients from a phase II study,[27] PR tacrolimus was associated with 4-year graft and patient survival rates of ~90%. As a complement to our previous study, we also evaluated the impact of crossover changes from IR to PR and vice versa after 1 month of induction therapy with regards to graft and patient outcomes. Both graft and patient survival were higher in patients who converted from IR to PR tacrolimus, compared with those who received induction PR tacrolimus and were still receiving PR tacrolimus at last follow-up. Although the cause of this is unclear, the data suggest that the use of PR tacrolimus at last follow-up therapy is associated with improved outcomes, irrespective of the timing of conversion. The transplant community is now interested in identifying whether earlier conversion (<6 mo after liver transplantation) from IR to PR tacrolimus is associated with better outcomes than conversion >6 months posttransplantation.[28]

The survival advantages observed in patients treated with PR versus IR tacrolimus reported at 3 years in Adam et al,[21] and at 4 years in this study were not observed in short-term, randomized, controlled trials. For example, Trunečka et al[29] reported 12-month graft survival rates of 85.3% and 85.6%, and patient survival rates of 89.2% and 90.8%, with PR and IR tacrolimus, respectively. The potential survival advantages associated with PR tacrolimus in de novo liver transplant recipients may, therefore, not become apparent until beyond 1-year posttransplantation.

In an independent editorial that accompanied the initial ELTR study, Asrani and O'Leary[30] considered the potential mechanisms underlying the improvement in long-term graft and patient survival with PR versus IR tacrolimus-based immunosuppression. Compared with IR tacrolimus, PR formulation reduces variability of tacrolimus exposure[19,31] and offers a simpler regimen comprising a single, morning dose,[12] which can improve medication adherence.[17,18] Indeed, in an expert literature review, improved adherence with treatment is highlighted as a main advantage of PR versus IR tacrolimus.[28] Given that high intrapatient variability in tacrolimus exposure and medication nonadherence have been associated with poor transplant outcomes,[8,20] PR tacrolimus may improve long-term graft and patient survival compared with the IR formulation.

As observed in the initial ELTR study,[21] the overall proportion of patients with graft loss was lower in the PR versus IR tacrolimus group. The reasons for graft loss and mortality were generally comparable between groups in this study and, consistent with the previous ELTR study, infections were the most frequent cause.[21]

In this study, not all factors could be controlled by the transplant team to improve outcomes. Only the type of preservation solution, the ischemia time, and the immunosuppressive regimen used could be altered, as donor and recipient characteristics cannot be changed in the MELD allocation system used in most countries. Therefore, it is important to consider the numbers of patients needed to treat with PR tacrolimus to avoid 1 graft loss. In this study, 14.3 patients needed to be treated with PR versus IR tacrolimus to avoid 1 graft loss in 4 years. These data are consistent with those of Muduma et al,[32] who developed a model using UK liver transplant data and showed that, over a 3-year time period, 1 graft would be saved for every 14 patients treated with PR versus IR tacrolimus, with minimal impact on costs. To place these data in clinical context, 15 patients needed to be treated with nicotine replacement therapy for 1 patient to cease smoking,[33] 20 required treatment with calcium and vitamin D for 3 years to prevent 1 hip fracture,[34] 23 required treatment with flu vaccine to prevent 1 flu episode,[35] and 35 needed primary treatment with statins for 5 years to prevent a cardiac event.[36]

Despite the improvements to our study design and analytical methods, any conclusions drawn from our findings must be made within the context of the limitations of our study, which have been described in detail previously.[21] These include the retrospective nature of the study and the long period over which data were collected, which may be associated with changes in clinical practice. Furthermore, our study design carries a risk of bias in terms of patient and treatment selection. To control for these differences, propensity score matching was undertaken against a larger number of characteristics compared with the initial ELTR study. However, it is recognized that propensity score matching can only be used to balance measured variables and cannot entirely exclude inherent differences, such as socioeconomic factors, ethnicity, or other unknown variables. A major limitation concerns the lack of data on drug exposure, as the dose and trough levels of tacrolimus were not captured in the ELTR; it is also not known which IR tacrolimus preparation patients were receiving. Despite these limitations, to our knowledge, we report on the largest population of liver transplant recipients to date, comparing the impact of PR and IR tacrolimus administration. Furthermore, this analysis builds on our previous publication by including a 3-fold larger cohort, providing extended follow-up, evaluating the impact of crossover between IR and PR tacrolimus therapy, and reporting the clinical implication of the results in terms of number needed to treat to avoid 1 graft loss.

Our results, based on up to 8-year data, confirm observations from the initial 3-year study[21] that PR tacrolimus-based immunosuppression can improve long-term outcomes in liver transplantation compared with IR tacrolimus. Furthermore, IR tacrolimus–based immunosuppression is a significant predictor of long-term graft loss and patient mortality. Conversion from IR to PR tacrolimus after 1 month was also associated with a better outcome compared with maintaining patients on IR tacrolimus–based immunosuppression, or starting and

maintaining patients on PR tacrolimus–based immunosuppression. Importantly, our findings confirm that PR tacrolimus continues to provide ongoing benefits for graft and patient survival beyond 3 years posttransplantation.

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